



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :  
Jacques JOLIVET et al. : Examiner: Cybille Delacroix-Muirheid  
Serial No.: 10/806,336 : Group Art Unit: 1614  
Filed: March 23, 2004 :  
For: METHOD FOR ADMINISTRATION OF TROXACITABNE

**DECLARATION BY HENRIETTE GOURDEAU UNDER 37 CFR §1.132**  
**REGARDING PUBLICATIONS BY NON-INVENTOR AUTHORS**

Commissioner for Patents  
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SIR:

I, Henriette Gourdeau, being duly warned, declare that:

I and Jacques Jolivet are the co-inventors of the claimed invention in the above-captioned application (see the attached list of claims).

I have been an employee of Shire BioChem Inc. since January 1995.

The instant application is assigned to Shire BioChem Inc.

I am a coauthor of the following publication: "Antitumor efficacy of troxacitabine given by continuous administration: The human HT-29 colon xenograft used as a tumor model," Proceedings of the American Association for Cancer Research, (1<sup>st</sup> Edition) Volume 44, Published March 2003, Abstract #2633.

The other authors listed on this publication are: Lorraine Leblond, Kelly Dong, Irenej Kianicka, Lucie Bibeau, Chantal Boudreau, Dominique Custeau, Lilianne Geerts, Annie Richard, Bettina Hamelin and Jacques Jolivet.

This publication relates to an in vivo study using rats, in which the feasibility of continuous infusion of troxacitabine was evaluated, which was performed for and under the direction, supervision and control of Shire BioChem Inc., and particularly under the direction, supervision and control of myself.

To the extent the claimed invention is disclosed in the above publication, coauthored by myself, Lorraine Leblond, Kelly Dong, Irenej Kianicka, Lucie Bibeau, Chantal Boudreau, Dominique Custeau, Lilianne Geerts, Annie Richard, Bettina Hamelin and Jacques Jolivet,

such disclosure is of mine and Jacques Jolivet's invention. The authors Lorraine Leblond, Kelly Dong, Irenej Kianicka, Lucie Bibeau, Chantal Boudreau, Dominique Custeau, Lilianne Geerts, and Annie Richard and Bettina Hamelin listed on the publication are not inventors, and contributed to aspects which were not part of the conception of the subject matter of the claims of this application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Henriette Gourdeau  
Henriette Gourdeau

Date: 22 Sept 05

**List of Claims:**

1. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours wherein a steady state plasma concentration of troxacitabine of 0.03 to 2.0  $\mu\text{M}$  is achieved during the administration.
2. A method according to claim 1, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, pancreatic cancer, renal cancer, hepatoma, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphomas.
3. A method according to claim 2, wherein said cancer is pancreatic cancer.
4. A method according to claim 1, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.
5. A method according to claim 4, wherein said cancer is acute myelogenous leukemia.
6. A method according to claim 2, wherein a steady state plasma concentration of 0.05 to 0.1  $\mu\text{M}$  is achieved during the administration.
7. A method according to claim 4, wherein a steady state plasma concentration of 0.1 to 0.42  $\mu\text{M}$  is achieved during the administration.
8. A method for the treatment of cancer within a patient, comprising administering to said patient an effective amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein the maximum plasma concentration achieved during the administration is 0.03 to 2.0  $\mu\text{M}$ .
9. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 1.0  $\mu\text{M}$ .
10. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.5  $\mu\text{M}$ .
11. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.42  $\mu\text{M}$ .

12. A method according to claim 8, wherein the maximum plasma concentration achieved during the administration is below 0.1  $\mu\text{M}$ .

13. A method for the treatment of cancer within a patient, comprising administering to said patient troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours at a dose of 0.72 to 12.5  $\text{mg}/\text{m}^2/\text{day}$ .

14. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 1.0 to 11.0  $\text{mg}/\text{m}^2/\text{day}$ .

15. A method according to claim 13, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 8.0 to 11.0  $\text{mg}/\text{m}^2/\text{day}$ .

16. A method according to claim 13, wherein said cancer is lung cancer, prostate cancer, bladder cancer, colorectal cancer, renal cancer, hepatoma, pancreatic cancer, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukemia or lymphoma.

17. A method according to claim 16, wherein said cancer is pancreatic cancer.

18. A method according to claim 13, wherein said cancer is acute myelogenous leukemia, chronic myelogenous leukemia, chronic myelogenous leukemia in blastic phase, or refractory myelodysplastic syndromes.

19. A method according to claim 18, wherein said cancer is acute myelogenous leukemia.

20. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 3.0  $\text{mg}/\text{m}^2/\text{day}$ .

21. A method according to claim 13, wherein said cancer is a solid tumor and the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5  $\text{mg}/\text{m}^2/\text{day}$ .

22. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof 9.5 to 10.5  $\text{mg}/\text{m}^2/\text{day}$ .

23. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 to 7 days.

24. A method according to claim 1, wherein said continuous infusion is administered for a period of 3 days.

25. A method according to claim 1, wherein said continuous infusion is administered for a period of 4 days.

26. A method according to claim 1, wherein said continuous infusion is administered for a period of 5 days.

27. A method according to claim 1, wherein said continuous infusion is administered for a period of 6 days.

28. A method according to claim 1, wherein said continuous infusion is administered for a period of 7 days.

29. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 3 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

30. A method according to claim 16, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 2.0 to 2.5mg/m<sup>2</sup>/day, said period is 4 days, and a steady state plasma concentration of 0.05 to 0.1 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

31. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 5 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

32. A method according to claim 18, wherein the dosage amount of troxacitabine or a pharmaceutically acceptable salt thereof is 9.5 to 10.5mg/m<sup>2</sup>/day, said period is 6 days, and a steady state plasma concentration of 0.1 to 0.42 μM of troxacitabine or a pharmaceutically acceptable salt thereof is achieved during the administration.

33. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 4 weeks.

34. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 3 weeks.

35. A method according to claim 1, further comprising repeating said continuous infusion at an interval of every 5 weeks.

36. A method according to claim 1 any one of the preceding claims, wherein said continuous infusion is by means of continuous intravenous infusion.

37. A method according to claim 1 any one of the preceding claims, wherein said method further comprising, in combination with said continuous administration of troxacitabine, administering at least one further therapeutic agent selected from the group comprising nucleoside analogues; chemotherapeutic agents; multidrug resistance reversing agents; and biological response modifiers.

38. A method according to claim 37, wherein said at least one further therapeutic agent is a chemotherapeutic agent selected from Asparaginase, Bleomycin, Busulfan, Carmustine, Chlorambucil, Cladribine, Cyclophosphamide, Cytarabine, Dacarbazine, Daunorubicin, Doxorubicin, Etoposide, Fludarabine, Gemcitabine, Gleevec®, Hydroxyurea, Idarubicin, Ifosfamide, Lomustine, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitomycin, Mitoxantrone, Pentostatin, Procarbazine, 6-Thioguanine, Topotecan, Vinblastine, Vincristine, Dexamethasone, Retinoic acid and Prednisone.

39. A method according to claim 37, wherein said at least one further therapeutic agent is the multidrug resistance reversing agent PSC 833.

40. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from monoclonal antibodies and cytokines.

41. A method according to claim 37, wherein said at least one further therapeutic agent is a cytokine selected from interferons, interleukins and colony-stimulating factors.

42. A method according to claim 37, wherein said at least one further therapeutic agent is a biological response modifier selected from Rituxan, CMA-676, Interferon-alpha recombinant, Interleukin-2, Interleukin-3, Erythropoetin, Epoetin, G-CSF, GM-CSF, Filgrastim, Sargramostim and Thrombopoietin.

43. A method according to claim 37 wherein said of troxacitabine or a pharmaceutically acceptable salt thereof and said at least one further therapeutic agent are administered sequentially.

44. A method according to claim 37 wherein said of troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered simultaneously.

45. A method according to claim 44 wherein said of troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in separate pharmaceutical formulations.

46. A method according to claim 44 wherein said of troxacitabine or a pharmaceutically acceptable salt thereof and at least one further therapeutic agent are administered in combined pharmaceutical formulations.

47. A method for the administration of troxacitabine or a pharmaceutically acceptable salt thereof in a host having a tumor, comprising administering an amount of troxacitabine or a pharmaceutically acceptable salt thereof by continuous infusion for a period of at least 72 hours, wherein said amount is sufficient to provide tumor reduction.